REMARKS

Amendments of claims 1-3 and 61-63.

Applicants have amended claims 1, and 61-63 by replacing "a" with "the"; claim 2 by replacing "its" with "the"; and claim 3 by inserting "the". The resulting "the complement(s)" from these amendments means the complements that are fully complementary to the "said nucleic acid(s)" in the respective claims. Although Applicants limit the literal scope of these claims in terms of the size of the complement, Applicants do not abandon any equivalents, which equity requires as necessary to protect the full scope of the claims, but may have not been claimed by the literal meaning of the claims because of the unforeseeable developments of the technology, or the inherent limitation of language to describe every small detailed variation.

Further, Applicants have amended claim 2 by inserting "of said nucleic acid"; claims 3, and 61-63 by replacing "thereof" with "of said nucleic acid". These amendments are only cosmetic changes to improve readability of the claims, and do not notice abandonment of any equivalents given by equity.

Amendments of claims 13 and 73-75.

Applicants have amended claims 13 and 73-75 by inserting "isolated" to exclude human beings as they are not patentable subject matter for now; however, Applicants do not abandon any equivalents, which equity requires as necessary to protect the full scope of the claims, but may have not been claimed by the literal meaning of the claims because of the unforeseeable developments of the technology, or the inherent limitation of language

to describe every small detailed variation. Further, Applicants do not abandon any patentable subject matter, which may have been excluded by the literal meaning of claims 13 and 73-75 by these amendments, and may be pursued for patents by subsequent continuation applications.

Rejection on claims 11-13 and 67-75 under 35 U.S.C. §112, ¶1.

The Examiner rejected claims 11-13 and 67-75 under 35 U.S.C. §112, ¶1 as the specification, while being enabling for isolated vectors and isolated host cells comprising said vectors, does not reasonably provide enablement for vectors and host cells comprised within a transgenic animal or an animal or human being having been treated by gene therapy. The Examiner also rejected claims 12 and 67-75 under 35 U.S.C. §112, ¶1 as the specification contemplates the use of the instant polynucleotides for the production of transgenic animals (pages 32-34) and in gene therapy (pages 42-45), but is not enabling for these uses since, in the Examiner's opinion, (A) with regard to gene therapy, the instant specification does not teach how to overcome problems with *in vivo* delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids, and *in vivo* gene delivery (as of our priority date) was not well developed and highly unpredictable, and (B) with regard to a transgenic animal, the instant specification does not provide guidance in the making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells, and, in the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable.

Applicants traverse the rejection. What are claimed are "vectors" in case of claims 11, and 67-69, and "expression vectors" in case of claims 12, and 70-72. The use of the claimed

vectors or expression vectors in gene therapy or transgenic animal generation is merely one of the many ways of using the claimed subject matter, not the claimed subject matter. Regarding claims 13 and 73-75, what are claimed are "host cells." The transgenic animals which may originate from the claimed host cells are a few among all possible embodiments of the claims. An application does not need to enable all possible embodiments that happen to fall within the scope of the claims to satisfy the enablement requirement, but what is required is that one of ordinary skill in the art is taught to practice the claimed invention with a reasonable expectation of success, which would include a reasonable amount of experimentation in order to pick and choose what would (or would not) work; therefore, Applicants believe that the application with the teachings explicitly written in the specification as well as those incorporated by reference enable the ordinary person skilled in the art to make and use host cells commensurate in scope with the claims 11-13 and 67-75 in terms of patent law.

Furthermore, Applicants believe that even the three references cited by the Examiner (Houdebine, *Journal of Biotechnology*, Vol. 34 (1994) pp. 269-287; Verma, *Nature*, 1997, Vol. 389, pp. 239-242; Eck, Gene-Based Therapy, In: *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, Ed.s, 1996, pp. 77-101) in fact show the adequacy of the knowledge level of the ordinary person skilled in the art at the time of filing, to utilize the claimed subject matter even for gene therapy or transgenic animal generation in case of claims 11, 12, and 67-72, or to make the host cells comprising transgenic animals in case of claims 13 and 73-75.

* Houdebine, *Journal of Biotechnology*, Vol. 34 (1994) pp. 269-287:

On page 4 of the Office Action, the Examiner paraphrases the first sentence of the paragraph bridging pages 272 and 273 of Houdebine, stating that "The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions ..." However, the passage in its entirety includes, in the next sentence, that "Many of such DNA sequences are now available, showing acceptably good specificity for a given cell type and in some cases, a high potency (emphasis added)." Thus, Houdebine merely proves that there were many appropriate regulatory regions available at the time of filing of the application that showed acceptably good specificity.

The Examiner also paraphrases a part of the first and second sentences of the first full paragraph on page 277, stating that "expression is heavily dependent on the site of integration in the host genome, and the site of integration is presently unpredictable." However, the passage in its entirety states that "Experiments carried out with transgenic animals soon revealed that in the great majority of cases, a transgenic expression is heavily dependent on its site of integration in the host genome rather than on the number of copies. The site of integration of a transgene is presently unpredictable when the DNA is microinjected into the pronuclei by the conventional method. This largely explains why the expression of a transgene in a given animal is also unpredictable (emphasis added)." From a reading of Houdebine, it can be reasoned that, at the time of filing of the application, not only were there successful occasions of transgenic expression but different systems had been characterized and compared.

* Verma, *Nature*, 1997, Vol. 389, pp. 239-242:

On page 3 of the Office Action, the Examiner paraphrases a passage on page 239 of the reference that "the Achilles heel of gene therapy is gene delivery... [and] the ongoing

problem is the inability to deliver genes efficiently and to obtain sustained expression (emphasis added)." Sustained expression is the incorporation of a transferred gene into the chromosome and the stability of the integrated gene, not the transfer of a gene into a cell. Further, the specification of the instant application teaches that "[i]f the transfected gene is not permanently incorporated into the genome of each of the targeted tumor cells, the treatment may have to be repeated periodically (page 43, lines 9-11, emphasis added)." A patent specification is not a production document. The reference states that "encouragingly, despite being repeatedly injected with highly concentrated recombinant viruses, the patients have suffered no untoward effects to date" (see page 242, second column, third full paragraph, emphasis added)

On page 239, in the second paragraph, Verma states that "[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" However, at page 242, in the first and second columns, the reference discusses the clinical trials in detail.

> "Over half of the 200 clinical trials that have been launched in the United States involve therapeutic approaches to cancer. Nearly 30 of them involve correction of monogenic diseases (Table 1) ... Most of the trials are phase I (safety) studies and, by and large, the existing delivery systems have no major toxicity problems. ... Clearly, in these cases the retroviral vectors were not optimal, and the number of infected blood-progenitor cells was extremely low. However, the trials did help to establish the technology for generating clinical-grade recombinant retroviral particles, the procedures for infection and transplantation, and the protocols for monitoring patients and analyzing data. The disappointing outcome probably lies in the inefficient gene-delivery

> system. We need a system in which the vector - containing ADA gene - delivered to progenitor cells, leading to sustained expression of high levels of the ADA for protein. But, encouragingly, despite being repeatedly injected with highly concentrated recombinant viruses, the patients have suffered no untoward effects to date (emphasis added)."

Thus, a reading of Verma et al. tells us there had so far been no successful result in terms of completion of a therapy, or an optimal vector, but confirms there were existing delivery systems that had no major toxicity problems and that more than 100 clinical trials had been carried out at the time of filing of the application. In addition, at that time, the technology for generating clinical-grade recombinant retroviral particles, the procedures for infection and transplantation, and the protocols for monitoring patients and analyzing data had already been established.

Further, Verma provides on page 241 criteria for selection of an ideal vector, and states on page 242 that "[a]ll of the available viral vectors arose from understanding the basic biology of the structure and replication of viruses. Clearly, existing vectors need to be streamlined further (see box page 241), and vectors that target specific types of cell are being developed (emphasis added)" (see page 242, second column, second full paragraph). Thus, Verma establishes that one of ordinary skill in the art was enabled to make and use the claimed invention (vectors) at the time of filing.

* Eck, Gene-Based Therapy, In: *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, Ed.s, 1996, pp. 77-101:

On page 3 of the Office Action, the Examiner paraphrases the fourth sentence of the paragraph bridging pages 81-82, stating "these factors differ dramatically on the vector used, the protein being produced, and the disease being treated." The word "dramatically" does not appear in the passage. The paragraph states in full, as follows:

> "The delivery of exogenous DNA and its processing by target cells require the introduction of new pharmacokinetic paradigms beyond those that describe the conventional medicines in use today (*see* Chapter 1). With *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, *etc.*), as well as for the consequences of altered gene expression and protein function. A multicompartmental model to describe these events in a quantitative fashion has been developed (Ledley and Ledlev. 1994). Processes that must be considered include the distribution of the DNA vector following *in vivo* administration; the fraction of vector taken up by the target cell population; the trafficking of the genetic material within cellular organelles; the rate of degradation of the DNA; the level of mRNA produced; the stability of the mRNA produced; the amount and stability of the protein produced; and the protein's compartmentalization within the cell, or its secretory fate, once produced. It is conceivable, although yet to be realized, that each of these events may be incorporated into the design of the gene transfer system in a rational way so as to tailor the gene transfer to the specific requirements of the disease being treated (emphasis added)."

Thus, according to Eck, the consideration is to establish a new pharmacokinetic paradigm, which is to develop a dosage formulation, and such a formulation had already been

established by Ledley and Ledley (1994). Further, the author alludes (in the last sentence of the above passage) that even an ideal vector may be designed.

To satisfy the enablement requirement, patent law does not require the ordinary person skilled in the art to practice the invention efficiently or to render the invention commercially viable, but only to make and use the claimed subject matter by picking and choosing what would (or would not) work through a reasonable experimentation, and the Applicants believe that the ordinary person skilled in the art, who has the knowledge of all relevant prior art including the Houdebine, Verma, and Eck articles, reading the application with the teachings from the explicitly written disclosures as well as the incorporated references, must be able to make and use the claimed subject matters of the claims 11-13 and 67-75 to the satisfaction of patent law.

In view of the amendments of claims 13, and 73-75, and the above remarks, Applicants submit that the rejection of claims 11-13 and 67-75 under 35 U.S.C. §112, ¶1 has been overcome, and request that the Examiner withdraw the rejection.

Rejection on claims 1-3 and 61-63 under 35 U.S.C. §102(b)

The Examiner rejected claims 1-3 and 61-63 under 35 U.S.C. §102(b) as being anticipated by New England Biolabs (1993/1994 Catalog). In view of the amendments of these claims, Applicants submit that the rejection on claims 1-3 and 61-63 under 35 U.S.C. §102(b) has been overcome. Specifically, it is submitted that "the complement" refers to a nucleic acid which is complementary to the entire specified nucleic acid and only means

complement. Thus, the prior art does not anticipate the claimed invention. Applicants respectfully request the Examiner withdraw the rejection.

In view of the above amendments and the remarks, the Applicants believe that the present application meets the requirements of the patent statutes, and is patentable over the prior art. Reconsideration of the application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned in order to expedite the prosecution of this application.

RESPECTFULLY SUBMITTED,			
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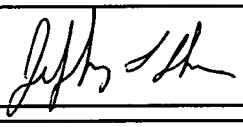
SIGNATURE		DATE	03 November 2003

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